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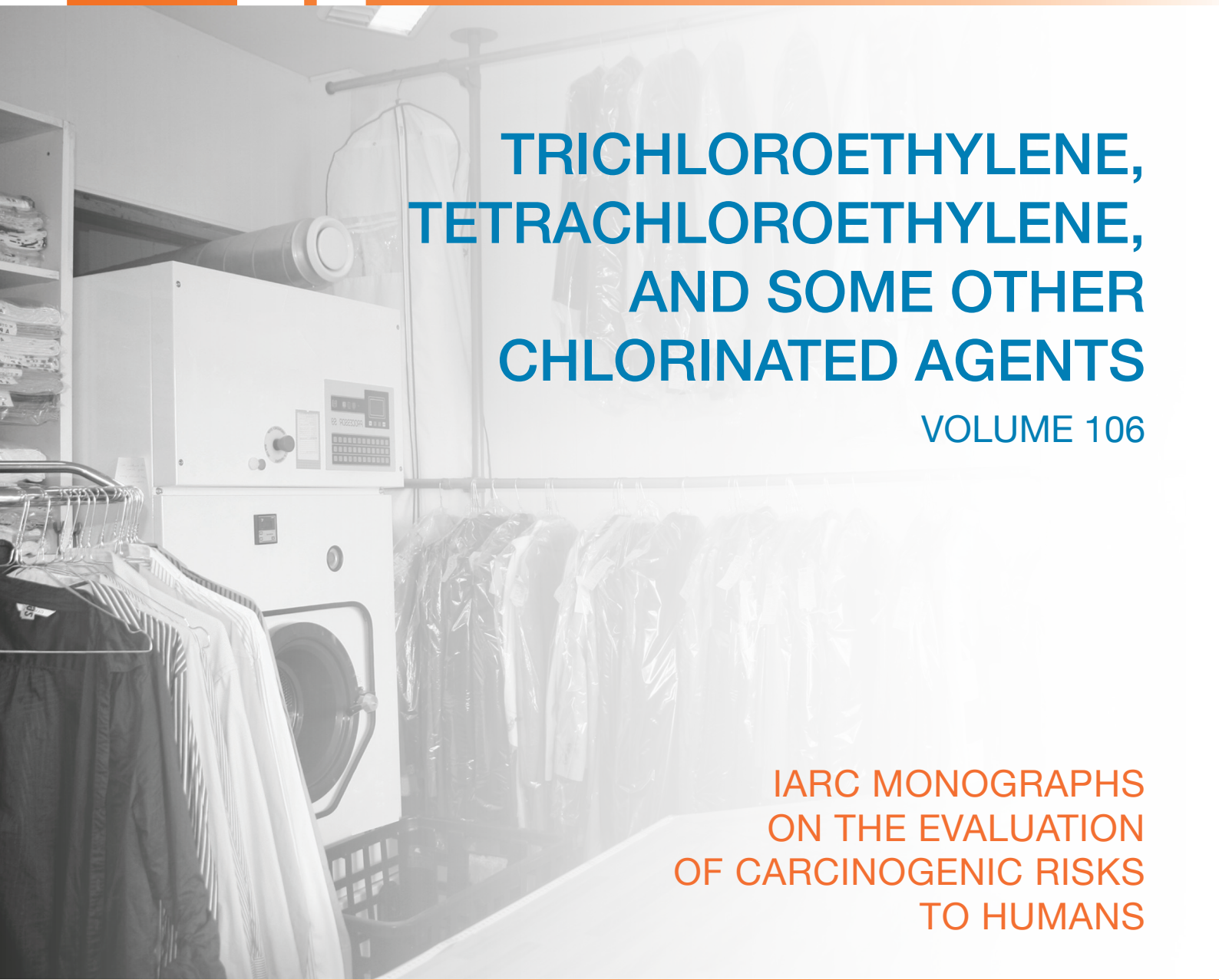
IARC MONOGRAPHS



TRICHLOROETHYLENE, TETRACHLOROETHYLENE, AND SOME OTHER CHLORINATED AGENTS

VOLUME 106

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer
World Health Organization

IARC MONOGRAPHS

TRICHLOROETHYLENE, TETRACHLOROETHYLENE, AND SOME OTHER CHLORINATED AGENTS

VOLUME 106

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 2-9 October 2012

LYON, FRANCE - 2014

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

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In 1969, the International Agency for Research on Cancer (IARC) initiated a programme on the evaluation of the carcinogenic risk of chemicals to humans involving the production of critically evaluated monographs on individual chemicals. The programme was subsequently expanded to include evaluations of carcinogenic risks associated with exposures to complex mixtures, lifestyle factors and biological and physical agents, as well as those in specific occupations. The objective of the programme is to elaborate and publish in the form of monographs critical reviews of data on carcinogenicity for agents to which humans are known to be exposed and on specific exposure situations; to evaluate these data in terms of human risk with the help of international working groups of experts in carcinogenesis and related fields; and to indicate where additional research efforts are needed. The lists of IARC evaluations are regularly updated and are available on the Internet at http://monographs.iarc.fr/.

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The term 'carcinogenic risk' in the *IARC Monographs* series is taken to mean that an agent is capable of causing cancer. The *Monographs* evaluate cancer hazards, despite the historical presence of the word 'risks' in the title.

Inclusion of an agent in the *Monographs* does not imply that it is a carcinogen, only that the published data have been examined. Equally, the fact that an agent has not yet been evaluated in a *Monograph* does not mean that it is not carcinogenic. Similarly, identification of cancer sites with *sufficient evidence* or *limited evidence* in humans should not be viewed as precluding the possibility that an agent may cause cancer at other sites.

The evaluations of carcinogenic risk are made by international working groups of independent scientists and are qualitative in nature. No recommendation is given for regulation or legislation.

Anyone who is aware of published data that may alter the evaluation of the carcinogenic risk of an agent to humans is encouraged to make this information available to the Section of IARC Monographs, International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 08, France, in order that the agent may be considered for re-evaluation by a future Working Group.

Although every effort is made to prepare the *Monographs* as accurately as possible, mistakes may occur. Readers are requested to communicate any errors to the Section of IARC Monographs, so that corrections can be reported in future volumes.

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Each participant was asked to disclose pertinent research, employment, and financial interests. Current financial interests and research and employment interests during the past 4 years or anticipated in the future are identified here. Minor pertinent interests are not listed and include stock valued at no more than US $1000 overall, grants that provide no more than 5% of the research budget of the expert's organization and that do not support the expert's research or position, and consulting or speaking on matters not before a court or government agency that does not exceed 2% of total professional time or compensation. All grants that support the expert's research or position and all consulting or speaking on behalf of an interested party on matters before a court or government agency are listed as significant pertinent interests.

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[2] Each Observer agreed to respect the Guidelines for Observers at IARC Monographs meetings. Observers did not serve as Meeting Chair or Subgroup Chair, draft any part of a Monograph, or participate in the evaluations. They also agreed not to contact participants before the meeting, not to lobby them at any time, not to send them written materials, and not to offer them meals or other favours. IARC asked and reminded Working Group Members to report any contact or attempt to influence that they may have encountered, either before or during the meeting.

[3] Observer for the American Chemistry Council. Paul Dugard was Director (until September 2011) of Halogenated Solvents Industry Alliance (HSIA), an Employment-Trade Association representing manufacturers of trichloroethylene and tetrachloroethylene. He is sole proprietor of PHD Consulting which consults for HSIA. His mutual fund includes stock in chemical companies. He is sponsored by HSIA.

[4] Observer for the European Chlorinated Solvents Association (ECSA). Gerard Swaen is employed by and holds stock in Dow Chemical company. He is sponsored by the European Chlorinated Solvents Association.

However, strong evidence of genotoxicity of DCVC, the metabolite of trichloroethylene in the kidney, supported an overall conclusion that the evidence of mechanisms of carcinogenesis in kidney is strong. There was strong evidence for liver as a target tissue for trichloroethylene from cancer and toxicity findings in experimental animals. The evidence for non-genotoxic and/or genotoxic mechanisms of liver carcinogenesis was moderate. The available data suggested that multiple non-genotoxic mechanisms of carcinogenesis exist, and that there is the potential for genotoxic mechanisms from trichloroethylene metabolites dichloroacetic acid and chloral hydrate. The evidence for the immune system as a target tissue for trichloroethylene from findings of a generalized hypersensitivity syndrome and of alterations of immune response in humans and experimental animals was strong. Evidence from studies in humans and experimental animals identifying active metabolites or the mechanisms for cancers of the immune system was weak, being limited to studies of immunological and haematological toxicity in humans and experimental animals. The evidence for the lung as a target tissue for trichloroethylene, from cancer and toxicity findings in experimental animals, was moderate. The data supporting the mechanisms of carcinogenesis in the lung were weak. The evidence for the nervous system as a target tissue for trichloroethylene on the basis of a variety of neurobehavioural effects in studies in humans and experimental animals was strong. The relevance of these effects to the potential cancer hazard of trichloroethylene in the nervous system is unknown. The data regarding the mechanism of carcinogenesis of trichloroethylene in the central nervous system were inconclusive. Trichloroethylene has been shown to adversely affect the male and female reproductive systems. The evidence for the male reproductive system as a target tissue for trichloroethylene was strong, on the basis of studies of toxicity in humans and experimental animals and studies of cancer in rats. The overall data supporting the mechanisms of carcinogenesis of trichloroethylene in the testes were weak, with limited data from humans and experimental animals available to support a mechanism involving hormonal disruption for trichloroethylene-induced testicular tumours. The overall support for an association between exposure to trichloroethylene and reproductive toxicity in females was weak.

The carcinogenicity and toxicity of trichloroethylene, particularly in the liver and kidney, are associated with its metabolism. Inter-individual differences in the formation of trichloroethylene metabolites that are thought to be responsible for toxic and carcinogenic effects of trichloroethylene in the kidney and liver exist in humans and rodents. Susceptibility to the adverse health effects of trichloroethylene may be influenced by genetics, sex, life stage and other conditions that influence the extent and nature of its metabolism. Polymorphisms in genes involved in oxidative metabolism (e.g. *CYP2E1*, *ADH*, *ALDH*) and glutathione conjugation (e.g. GSTs) have been studied in connection with susceptibility to toxicity and carcinogenicity caused by trichloroethylene. Polymorphisms in genes for plasma-membrane transporters (e.g. *OAT1* and *OAT3*) may also influence rates or extent of cellular accumulation of key metabolites. With respect to life-stage susceptibility, data were available to support conclusions concerning differences in exposure (e.g. transplacental transfer or exposure through breast milk in early life stages) or life-stage-specific differences in toxicokinetics. Lifestyle factors (e.g. consumption of alcoholic beverages) may also affect the metabolism of trichloroethylene, while nutrition or obesity may affect internal concentrations of trichloroethylene and its metabolites.

6. Evaluation

6.1 Cancer in humans

There is *sufficient evidence* in humans for the carcinogenicity of trichloroethylene. Trichloroethylene causes cancer of the kidney. A positive association has been observed between exposure to trichloroethylene and non-Hodgkin lymphoma and liver cancer.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of trichloroethylene.

6.3 Overall evaluation

Trichloroethylene is *carcinogenic to humans (Group 1).*

6.4 Rationale

The Working Group was unanimous in its conclusion that trichloroethylene is a Group 1 carcinogen.

The majority of the Working Group concluded that the epidemiological data were sufficient; however, a minority had concerns because most of the positive evidence came from case–control studies, while the data from cohort studies were weaker.

In reaching unanimous agreement, the Working Group took into consideration the following supporting evidence:

- The absorption, distribution, metabolism and excretion of trichloroethylene are well characterized in experimental animals and humans.
- In experimental animals and humans, oxidative metabolism of trichloroethylene is catalysed by cytochrome P450 enzymes and GSH conjugation of trichloroethylene is catalysed by GST enzymes.
- The formation of reactive metabolites of trichloroethylene in the kidney from processing of GSH-conjugation metabolites in situ has been observed in experimental animals and in human kidney cells.
- The reactive GSH-conjugation metabolites of trichloroethylene are genotoxic on the basis of consistent results in several available test systems.

Consistent with the importance of the GSH-conjugation metabolic pathway for kidney carcinogenesis, one study demonstrated a statistically significant association among trichloroethylene-exposed people with at least one intact *GSTT1* allele, but not among those with two deleted alleles.

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LIST OF ABBREVIATIONS

2,4-D	2,4-dichlorophenoxyacetic acid
2,4,5-T	2,4,5-trichlorophenoxyacetic acid
5MeC	5-methylcytosine
8-OHdG	8-hydrodeoxyguanosine adducts
ADH	alcohol dehydrogenase
ALDH	aldehyde dehydrogenase
ALT	alanine transferase
AST	aspartate transferase
AUC	area under the concentration–time curve
BEI	biological exposure index
bw	body weight
CAREX	CARcinogen EXposure
CBI	covalent binding index
CCBL	cysteine-conjugate β-lyase
CI	confidence interval
coA	coenzyme A
CYP450	cytochrome P450
DCVCS	*S*-(1,2-dichlorovinyl)-L-cysteine sulfoxide
DCVT	*S*-(1,2-dichlorovinyl)-thiol
DDT	dichlorodiphenyltrichloroethane
DMSO	dimethyl sulfoxide
ECD	electron capture detection
ENU	*N*-ethyl-*N*-nitrosourea
EPA	Environmental Protection Agency
EU	European Union
FDA	Food and Drug Administration
FID	flame ionization detection
FMO	flavin-containing monooxygenase
GC	gas chromatography
GGT	γ-glutamyltranspeptidase OR γ-glutamyltransferase???
GSH	glutathione
GST	glutathione-*S*-transferase
GTK	glutamine transaminase K
HDL	high-density lipoprotein
HECD	Hall electrolytic conductivity detection

HR	hazard ratio
LD_{50}	median lethal dose
LOH	loss of heterozygosity
MCD	microcoulometric detection
MNNG	*N*-methyl-*N*′-nitro-*N*-nitrosoguanidine
MNU	*N*-methyl-*N*-nitrosourea
MS	mass spectrometry
NA	not applicable
NAcDCVC	*N*-acetyl-*S*-(1,2-dichlorovinyl)-L-cysteine
NADH	nicotinamide adenine dinucleotide
NADPH	nicotinamide adenine dinucleotide phosphate
NAG	*N*-acetylglucosaminidase
ND	not detected
NHL	non-Hodgkin lymphoma
NIOSH	National Institute for Occupational Safety and Health
NR	not reported
NS	not significant
NTP	National Toxicology Program
OEL	occupational exposure limit
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PBN	phenyl-*tert*-butyl nitroxide
PID	photoionization detection
PPARα	peroxisome proliferator-activated receptor alpha
ppm	parts per million
ppt	parts per trillion
RR	relative risk
S9	9000 × *g* supernatant
SCOEL	Scientific Committee on Occupational Exposure Limits
SD	standard deviation
SIR	standardized incidence ratio
SMR	standardized mortality ratio
SSB	single-strand DNA break
SSCP	single-stand conformation polymorphism
TBARS	thiobarbituric acid-reactive substances
TLV	threshold limit value
TWA	time-weighted average
UDS	unscheduled DNA synthesis
USP	United States Pharmacopeia
vs	versus